REMARKS

In the Office Action dated December 11, 2002, Claims 1-27 are pending. The Examiner has made the restriction requirement final. Therefore, Claims 1-10 and 16-27 are currently under consideration. Claims 24 and 25 have been rejected under 35 U.S.C. § 101, as allegedly improper. Claims 1-3, 5-10 and 16-27 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enabling support. Claims 3, 4, 16-21 and 24-27 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

This response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 11-15 have been withdrawn from the consideration. Applicants reserve the right to file one or more divisional applications directed to the subject matter of Claims 11-15.

Claims 24 and 25 have been rejected under 35 U.S.C. § 101, as allegedly improper. Specifically, the Examiner contends that the claimed recitation of a use, without setting forth any steps involved in the process, is an improper definition of a process under United States patent law.

In response, Applicants have amended Claims 24 and 25 and added Claims 28-34. Support for the amendment and the newly added claims can be found throughout the specification and at page 15, line 26 to page 16, line 15, and in the original Claims 24-25. No new matter has been added. Claims 24-25, as amended, and the newly added Claims 28-34 are in compliance with 35 U.S.C. § 101. Therefore, the rejection of Claims 24-25 under 35 U.S.C. § 101 is overcome and withdrawal thereof is respectfully requested.

Claims 1-3, 5-10 and 16-27 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enabling support. Specifically, the Examiner contends that the specification, while enabling for two χ-conotoxin peptides, χ-MrIA and χ-MrIB, having the ability to inhibit a neuronal amine transporter, does not provide enablement for the claimed variants and methods for treatment. The Examiner contends that undue experimentation is required to practice the invention.

In the first instance, Applicants observe that conotoxin peptides are relatively short peptides, typically containing 12 to 30 amino acids, which are present in the venom of marine snails of the genus *Conus* (cone snails). As indicated in the specification on page 1, lines 15-16, the venom from any single *Conus* species may contain more than 100 different peptides.

Applicants observe that the specification teaches, for example, on page 1, lines 16 to 27, that the conotoxin peptides are classified according to their physiological targets. Significant work has been done over the last 20 years to characterize peptides isolated from *Conus* venoms and up until the filing date of the present application, 10 different classes had been described in the literature.

Applicants also observe that the specification teaches that conotoxin peptides of a particular class are also generally related by the pattern and number of cysteine residues and the disulphide based connectivity between those cysteine residues. *See* specification, at page 11, lines 25-27 and page 15, lines 9-15, for example. It is also known in the art that, ω-conotoxins are characterized by having six cysteine residues forming three disulphide bonds with an A-D/B-E/C-F pattern of connectivity, while α-conotoxins characteristically have cysteine residues forming two disulphide bonds with an A-C/B-D pattern of connectivity. The pattern of disulphide bonds confers distinct structure upon the peptide. Thus conotoxin classes are

characterized by a combination of activity and structure. Applicants are willing to provide references supporting the structural characterization of conotoxins upon the Examiner's request.

Applicants respectfully submit that, despite all the research conducted in relation to peptides isolated from cone snails, the prior art has failed to identify or describe conotoxin peptides which inhibit neuronal amine transporters. Similarly, the prior art does not provide any class of conotoxins characterized by four cystine residues with A-D/B-C disulphide connectivity. In view of the fact that the conotoxin peptides according to the present invention act at a different physiological target than the conotoxin peptides previously described, the peptides must, by convention, be classified as a new class. The inventors have selected the Greek symbol χ to designate this new class of conotoxin peptides.

Applicants further submit that once a member of a new class of conotoxin peptide is identified, routine molecular biology techniques can be used to design probes to identify other peptides of that class. These techniques have been used widely to identify other members of previously described classes of conotoxin peptides. Also, once the activity of a class of conotoxin peptides has been determined, it is possible to use assay guided fractionation techniques, e.g., as exemplified in Example 5, to identify other conotoxin peptides of that class in isolated venoms.

The Examiner alleges that the specification lacks working examples of claimed variants other than χ-MrIA. Applicants respectfully submit that the inventors have now obtained additional data regarding the preparation and function of χ-conotoxin derivatives, other than χ-MrIA and χ-MrIB. These derivatives have been tested in an assay corresponding to the assay described in Example 5 to compare the potency of the derivatives to χ-MrIA. Examples of such derivatives are as follows:

pGlu Gly Val Cys Cys Gly Tyr Lys Leu Cys His Hyp Cys
pGlu Gly Val Cys Cys Gly Tyr Lys Leu Cys His Hyp Cys
pGlu Gly Val Cys Cys Gly Tyr Lys Leu Cys His Hyp Cys
pGlu Gly Val Cys Cys Gly Tyr Lys Leu Cys His Hyp Cys
pGlu Gly Val Cys Cys Gly MeY Lys Leu Cys His Hyp Cys
pGlu Gly Val Cys Cys Gly MeY Lys Leu Cys His Hyp Cys
pGlu Asp Gly Val Cys Cys Gly MeY Lys Leu Cys His Hyp Cys[1]
pGlu Asp Gly Val Cys Cys Gly MeY Lys Leu Cys His Hyp Cys
pGlu Asp Gly Val Cys Cys Gly Tyr Lys Leu Cys His Hyp Cys

The Examiner alleges that the specification provides insufficient disclosure in relation to how the claimed peptides would be used in the described treatments. The Examiner alleges that general knowledge and level of skill in the art do not supplement the omitted description. The Examiner further contends that compounds useful for treating lower urinary tract disorders in the prior art cited by the specification are small molecules which are structurally different from χ-conotoxin peptides.

In response, Applicants submit that peptides and small molecules have many features in common, including stability and biological activity. In fact, peptides often have greater potency and selectivity than nonpeptidic small molecules. For example, peptidic inhibitors of hepatitis C-NS3 protease are far more potent and selective than their small molecule counterparts (Leung et al., 2000; J. Med. Chem 43(3), 305-341), as it is impossible for the small molecule to make the same number of contacts with the target to achieve the required selectivity for a clean drug. In the example given above, the small molecules also inhibit a number of other proteases including chymotrypsin, trypsin, plasmin and elastase, whereas the peptide inhibitors do not. Lack of selectivity often leads to serious side-effects, therefore despite issues of delivery, peptides are now attractive drug candidates.

[1] MeY refers to 4-methoxy tyrosine.

Applicants also submit that peptides may at times necessitate specific forms of delivery. However, similar special delivery techniques are at times also required for small molecules. Thus, there is clear and virtually complete overlap in the therapeutic potential of peptides and small molecules. In fact, the literature is replete with evidence of the overlap of the pharmacological activity of peptides and a small organic molecules. For example, there are a number of known ω-conotoxins that inhibit the N-type voltage-sensitive calcium channels and as such are known to be useful in the treatment of pain and providing neuroprotection in global ischemia. *See* O'Neil et al. (1997) Eur. J. Pharmacol. 332, 121-31. Similarly, a number of small molecules have been found that are N-type VSCC blockers and also have similar neuroprotective effects. *Id.* In another example, well known sodium channel blockers, tetrodotoxin and saxitoxin, have similar activities to a group of peptides called μ-conotoxins (i.e., GIIIA-C). Here, both sets of compounds target the same site on the outer vestibule of the voltage-sensitive sodium channel and elicit similar effects. *See, e.g.,* Yanagawa et al. (1988) *Biochemistry* 27, 6256-6262 (identification of μ-conotoxin peptides, CGIIIA, CGIIIB and conotoxin GS as competitive inhibitors of small molecules tetrodotoxin (TTX) and saxitoxin (STX) at the voltage-sensitive Na channel); Marban et al. "Structure and function of voltage-gated sodium channels" *J. Physiology* (1998) 508.3, 647-57 (a review on sodium channels which discloses (on page 652, paragraph 2) the overlap of the binding site of μ-conotoxin peptides and STX and TTX).

Further evidence of the efficacy of the claimed conotoxin peptides can be found in an *in vitro* study which evaluated the ability of small molecules and related conotoxin peptides to inhibit noradrenaline transporters. Using a *vas deferens* model, both small molecules and peptides inhibited the noradrenaline transporters and increased the strength of the second phase

of electrically induced contractions. Applicants can provide further evidence regarding the described study upon request.

Therefore, results associated with small molecules with a particular mode of action, e.g. noradrenaline transporter inhibition, can be extrapolated directly to peptides with the same essential pharmacology. Applicants therefore submit that small molecule inhibitors of noradrenaline reuptake have the same type of effects *in vivo* as their peptide counterparts.

Applicants further direct the Examiner's attention to the specification which provides examples showing that inhibitors of monoamine reuptake, and in particular inhibitors of noradrenaline reuptake, have therapeutic use in the treatment of pain, mood disorders and disorders of the lower urinary tract. The evidence of the assays used in the examples is appropriate for predicting therapeutic activity.

Thus, Applicants respectfully submit that, given the teaching, guidance and working examples provided by the specification, a skilled person can make other χ-conotoxins or derivatives thereof and use the claimed variants for the treatment of urinary or cardiovascular diseases and conditions or mood disorders, without undue experimentation. For example, the specification teaches: the preparation of χ-conotoxin, e.g., on page 2, line 16-26; generation of χ-conotoxin derivatives, e.g. on page 4, line 9 to page 13, line 6; the ability of χ-conotoxin or derivatives thereof to inhibit a neuronal amine transporter, e.g. on page 1, line 29 to page 2, line 1; that compounds, which inhibit neurotransmitter reuptake, have been found useful in the treatment of lower urinary tract disorders, e.g. on page 2, lines 3-9; that χ-conotoxin peptides and derivatives thereof can be used for treatment of urinary or cardiovascular disorders, or mood disorders, e.g. on page 16, line 5 to page 17, line 4; dosage and the administration routes for the treatment, e.g. page 17, line 6 to page 20, line 24; examples regarding the inhibition of the

accumulation of radioactive labeled noradrenaline by χ-MrIA in animals,. *e.g.*, in Example 5 (pages 28-29); comparability of small molecule and peptides in stability and biological activity. Applicants also submit that the inventors posses data that shows the effects of χ-conotoxins in a rat model of neuropathic pain. In an experiment as described in Exhibit A, the inventors demonstrated that χ-conotoxin (MrIA) produced the same dose-dependent antinociceptive effect as morphine in a rat model. The experiment also demonstrated that MrIA produced produced antinociceptive effects that lasted at least as long as morphine.

Moreover, Applicants submit that, 35 U.S.C. § 112 does not require that an inventor provide examples and conditions for every use of the claimed invention. Accordingly, the rejection of Claims 1-3, 5-10 and 16-27 under 35 U.S.C. § 112, first paragraph, is overcome and withdrawal thereof is respectfully requested.

Claims 3, 4, 16-21 and 24-27 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite.

Specifically, the Examiner contends that Claims 3 and 4 are indefinite for reciting "one or more amino acid deletions, additions, substitutions or side chain modifications." The Examiner contends that it is not clear which amino acids are deleted, added, substituted or modified and what amino acid sequences are obtained after modification. The Examiner also contends that it is not clear what amino acid, recited as "O" in Claim 3, is referred to.

In response, Applicants respectfully direct the Examiner's attention to page 3, line 13, where "O", as recited in SEQ ID NO:1 and 2, is referred to as "4-hydroxy proline (Hyp)."

With respect to the recitation "one or more amino acid deletions, additions, substitutions or side chain modifications," Applicants observe that the specification, teaches that peptides can tolerate significant changes while still retaining activity (see Examples 5-7).

Applicants also observe that Claim 3 includes a functional recitation and the specification provides assays for testing function or activity. Furthermore, methods guiding amino acid deletions, additions, substitutions or side chain modifications are disclosed in the specification, e.g., on page 4, line 9 to page 13, line 6. Therefore, Applicants submit that the specification provides clear disclosure for a person skilled in the art to conduct the modification of the claimed peptides.

The Examiner also alleges that Claim 16 is indefinite because it is not clear which biologically active peptide or protein is intended, which segment of the χ-conotoxin peptide or other peptide is used, whether the segment of the χ-conotoxin peptide or the other peptide is still biologically active, and which activity the resultant χ-conotoxin peptide possesses.

In response, Applicants have amended Claim 16. Support for the amendment can be found throughout the specification, e.g., on page 15, lines 17-18 and original Claim 16.

The Examiner further contends that Claims 17-21, 26 and 27 are indefinite as lacking essential steps in the method of treatment. The Examiner states that the omitted steps are: the method of administration and the outcome of the treatment. Claims 18-21 have been rejected for their dependencies on Claim 17.

Applicants submit that Claim 17 includes the step of administration of a χ-conotoxin peptide having the ability to inhibit neuronal noradrenaline transporters for the treatment of urinary or cardiovascular conditions or mood disorders. Therefore, the recitation of "treatment," in fact, indicates the outcome, i.e. the pathological condition is inhibited, reduced, or eliminated. Applicants respectfully submit that the method of administration is not required in a treatment claim. However, in an effort to expedite favorable prosecution, Applicants have amended Claim 17 to recite the administration routes. Applicants have also amended Claims 26-27. Support for

the amendment can be found throughout the specification, e.g., on page 18, lines 13-14 and 26, page 19, lines 21-27.

The Examiner also contends that Claims 24 and 25 are indefinite for not including any active steps. The Examiner finally contends that Claims 26 and 27 are indefinite for reciting the term "diseases and conditions." Applicants believe that these rejections have been obviated by the amendment to Claims 24-27 and the addition of Claims 28-34.

Accordingly, the rejection of Claims 3, 4, 16-21 and 24-27 under 35 U.S.C. § 112, second paragraph, is overcome and withdrawal thereof is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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Encl: Exhibit A